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Original Research

What impact does therapy selection have on the course of clinical outcomes for recurrent gliomas?

Treatment selection in recurrent gliomas

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Abstract
Aim: The aim of this study is to investigate the effectiveness of systemic treatments in patients with recurrent glioblastoma (GBM), and to assess their impact on overall survival (OS) and progression-free survival (PFS). Despite multimodal treatment approaches, GBM remains a challenging malignancy, and this study aims to contribute to understanding the treatment outcomes and factors influencing prognosis.
Materials and Methods: Twenty patients with recurrent gliomas were included in the study out of the 133 patients who had a glioma diagnosis between 2015 and 2021.
Results: Relapses occurred on average after 30.1 (range: 5.7-182.6) months. The average patient age upon diagnosis was 51 (range: 24-68). Males made up 65% of the patients. Systemic treatment was given to 17 individuals (85%). 70.5% of patients preferred the bevacizumab+irinotecan (BEV+IRI) regimen as their first-line treatment. Carmustine (5.5%) and temozolomide rechallenge (23.5%) were the other regimens. Patients who underwent systemic treatment following a relapse had an average overall survival of 8.1 months. 53.8% was the 6-month OS for patients following recurrence.
Discussion: Consequently, these patients have low systemic treatment effectiveness. The influence of the proposed treatment on performance status and quality of life should be taken into account, regardless of the severity of the disease. A less risky regimen or active surveillance may be beneficial for patients with gliomas that do not show targetable pathological alterations, as there was no statistically significant difference seen when progression-free survival lengths were evaluated.

Keywords
Glioma, Recurrence, Systemic Therapy, Overall Survival, Chemotherapy

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Introduction

In oncology, gliomas are among the malignancies with the worst prognoses. Even with the current treatments recommended in the guidelines, the average survival for high-grade gliomas is 15 months, and the 2-year survival rate is 26-33% [1]. To optimize the treatment protocol, a deeper comprehension of the cellular, molecular, and intercellular pathophysiology of gliomas is needed. There are several different treatment choices available at the moment of diagnosis, including radiation, chemotherapy, and surgical resection [2]. Despite ongoing research efforts to devise novel therapeutic approaches, aggressive, treatment-resistant recurrences of original glioblastomas are the inevitable outcome. Research has been done to determine whether and how therapies affect the molecular characteristics, growth pattern, and intratumoral heterogeneity of glioblastoma, as well as the degree to which this knowledge can be applied to therapeutic decision-making [3, 4]. We shared the post-recurrence treatments and survival analyses of our clinic's glioma patients because we wanted to add to the body of knowledge on the management and therapy protocol for these uncommon malignant brain tumors.

Materials and Methods

Patients treated at our hospital who were diagnosed with gliomas were the subjects of a retrospective investigation. Twenty patients with recurrent gliomas were included in the study out of the 133 patients who had a glioma diagnosis between 2015 and 2021. Information was gathered from the patient's records and documentation. Inclusion criteria: being over 18 years of age and being diagnosed with recurrent glioma. Exclusion criteria: Being a pediatric case under the age of 18 and having accompanying secondary malignancies. Analysis was done on the patient's age, operation status, date of recurrence, pathological characteristics, status of reoperation and reirridation, and systemic treatments received following recurrence. Progression-free survival (PFS) was determined using the date on which patients made treatment-related progress; overall survival (OS) was computed using the date of the final follow-up, or ex-date. Pathological aspects of the tumor were EGFR, IDH mutation, grade, and histology. After revision, the data were tallied and examined. The data were analyzed with the SPSS 22 software, and a p value below 0.05 was considered significant.

Ethical Approval

This study was approved by the Ethics Committee of Ege University, Faculty of Medicine (Date: 2024-02-20, No: 2024-2393).

Results

The study comprised 20 patients with recurrent gliomas. 65% of the patients were male. Relapses occurred on average after 30.1 (mean±SD (%95 CI): 45,25±12.78; range: 5.7-182.6) months. The average patient age upon diagnosis was 51 (mean±SD (%95 CI) 47,38±12,98; range: 24-68). Males made up 13 (65%) of the patients. The local treatments that patients received after recurrence are summarized in Figure 1. Grade 4 histology was present in 11 (55%) of the patients with glioblastoma multiforme. 4 (20%) had grade 3 anaplastic astrocytomas. Among them, IDH mutations made up 8 (40%). 11 patients (55%) underwent additional surgery. Six patients (30%) underwent reirradiation. Three individuals (15%) tested positive for an EGFR mutation; these patients were considered for treatment with nimotuzumab. 2 patients (10%) had a 1p19q deletion. Grade 4 tumors were found in 11 (55%) of patients, grade 3 tumors in 4 (20%), and grade 2 tumors in 3 (15%) of patients. The pathological and clinical characteristics of patients are summarized in Table 1.

Systemic treatment was given to 17 (85%) individuals. 12 (70.5%) patients preferred the bevacizumab+irinotecan (BEV+IRI) regimen as their first-line treatment. 1 patient (5.5%) received carmustine, and 4 patients (23.5%) received temozolomide rechallenge; the rest were other regimens (Figure 2). Patients on BEV+IRI in the first line had an average PFS of 5.82 months. Four patients who received temozolomide challenge as first-line treatment had an average progression-free survival of six months. After receiving carmustine as the initial line of treatment, one patient made progress in 3.1 months. The mean PFS of treatments given in the first line are

Table 1. Clinicopathological characteristics of patients

Parameter	Value
Age at diagnosis (median/range)	51 (24-68)
mean±SD	47,38±12,98
Male	13 (65%)
Female	7 (35%)
Relapse time (median/range)	5.7-182.6 months
mean±SD	45,25±12.78
Diagnostic histology, n (%)	20 (100%)
Glioblastoma multiforme	11 (55%)
Grade 3 anaplastic astrocytoma	4 (20%)
Grade 2 astrocytoma	3 (15%)
Oligodendroglioma	2 (10%)
Pathological findings, n (%)	20 (100%)
Grade 4 tumors	11 (55%)
Grade 3 tumors	4 (20%)
Grade 2 tumors	3 (15%)
1p 19q codeletion, n (%)	2 (10%)
IDH mutation, n (%)	8 (40%)
EGFR mutation , n(%)	3 (15%)
Chemotherapy regimens, n (%)	17 (100%)
BEV+IRI	12 (70.5%)
Temozolomide	4 (23.5%)
Carmustine	1 (5.5%)
Overall survival (OS)	
Average OS	8.1 months
Six month OS	53.8%

Table 2. Median PFS comparison of first-line treatment regimens

First line treatment regimen	n (%)	Median PFS (min-max) (months)
BEV+IRI	12 (70.5%)	5.82 (0.3-21.9)
Temozolamide	4 (23.5%)	6 (1.47-16.83)
Carmustine	1 (5.5%)	3.1

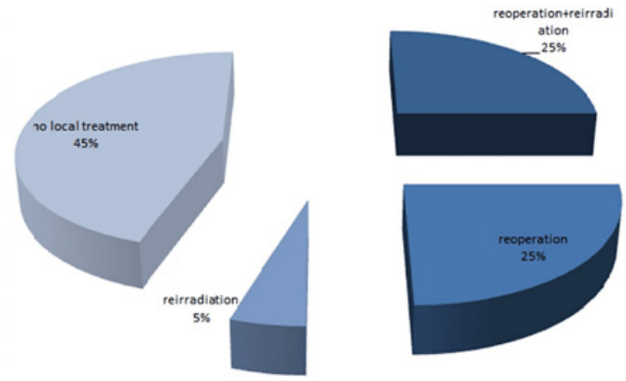

Figure 1. Local treatments for recurrence

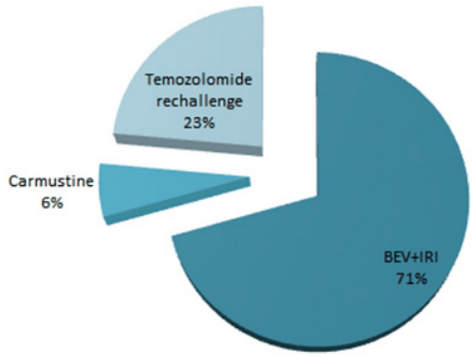

Figure 2. First line systemic therapy of patients

summarized in Table 2. Carmustine was moved to the second line following BEV+IRI in 2 patients, and the average PFS was determined to be 3.7 months. On the third line, nimotuzumab was started for one patient; nevertheless, the patient's PFS was only one month. Patients who underwent systemic treatment following a relapse had an average overall survival of 8.1 months. 53.8% was the 6-month OS for patients following recurrence.

Discussion

Treatment selection for recurrent GBM is a clinical problem that requires consideration of multiple aspects. Nearly all GBM patients are predicted to experience tumor recurrence; yet, very few salvage therapies have shown any efficacy thus far [4]. This challenge results from confounding variables in imaging and molecular heterogeneity, which is believed to be treatment-related as well as spontaneous [4, 5]. Certain individuals may just need supportive care or systemic medications, even if locoregional therapies may be the best course of action in certain situations. Reoperation and reirradiation, along with systemic treatments like procarbazine, vinca alkaloids (vincristine), nitrosoureas (carmustine/lomustine/fotemustine), platinums, topoisomerase inhibitors (irinotecan/etoposide), antiangiogenic bevacizumab, and their combinations, are all used to treat recurrent GBM [6]. Regorafenib is a small-molecule tyrosine kinase inhibitor with inhibitory efficacy against numerous targets implicated in tumor angiogenesis and oncogenesis. It can be administered to patients with recurrent glioblastoma as a first-line systemic treatment. Regorafenib significantly improved OS compared to the lomustine group in phase 2 research that was carried out in Italy and examined the efficacy of the drug in patients with recurrent glioblastoma (OS of 7•4 months (95% CI 5•8-12•0) (7). As with non-small cell lung cancer (targeting mutations like ALK and EGFR) and breast cancer (targeting HER2 overexpression), individualized treatment trials are still in progress. NTRK inhibitors when adult gliomas have fusions of the NTRK gene; the guidelines cover the use of entrectinib and larotrectinib [7, 8]. BRAF+Mek inhibitors Vemurafenib/cobimetinib and Dabrafenib/trametinib are utilized when the BRAF V600E mutant is present [9, 10]. There were no patients using targeted agents in our study. Before beginning normal systemic therapy for recurring diseases, it is crucial to assess clinical studies. Survival is still poor even after recurrent GBM is removed, and there isn't any evidence to support the idea that surgery is any more beneficial than reirradiation and/or salvage chemotherapy. Resection covering more than 80% of the recurrent GBM volume resulted in an OS advantage (19 months), according to a retrospective study [11]. According to prospective research, individuals with recurrent illnesses who underwent several microsurgical resections had a greater overall survival (OS) than patients who started systemic medication without surgery [12].

Reirradiation is now a viable treatment option for patients with brain tumors due to advancements in radiotherapy technology. This is especially true for patients with recurrent GBM. There is insufficient data on the utilization of reirradiation with bevacizumab (BEV), temozolomide (TMZ) rechallenge, or immune checkpoint inhibition (ICI) therapy [13]. When compared to radiation alone, concurrent radiotherapy and/or adjuvant therapy with TMZ produced prolonged OS and PFS durations; however, this was typically restricted to MGMT-methylated tumors [14, 15]. There was no discernible survival advantage in certain investigations [16, 17]. Roughly 90% of WHO grade IV gliomas (GBM) will recur locally within 2 years, despite rigorous management that involves maximally safe surgical resection followed by external beam radiation therapy (60 Gy/30 fractions) with concurrent and adjuvant TMZ. Numerous studies have demonstrated that patients with recurrent GBM who receive stereotactic radiosurgery (SRS) or stereotactic radiotherapy (SRT) with the help of hypofractionated or conventionally fractionated schedules have an increased chance of survival after reirradiation. Nevertheless, questions remain regarding the safety and efficacy of a second radiation course. In one trial, both treatment modalities had a comparable median overall survival and a comparatively low toxicity profile, lasting between six and twelve months [13]. According to international standards, young patients with good performance status who have progressive or recurrent GBM should be considered for reirradiation, particularly if it has been a long time since previous radiation therapy [4]. Patients who got reirradiation in our study ranged in age from 37 to 68 years old, with an average PFS of 4.6 months. Three patients received BEV+IRI following progression, two patients received TMZ rechallenge, and one patient received carmustine.

The possible superiority of concurrent/adjuvant systemic therapy plus reirradiation over systemic therapy alone is another crucial question that needs to be answered. Tsien et al. assessed the safety and effectiveness of bevacizumab alone versus hypofractionated SRT and concurrent bevacizumab in a phase II randomized study involving 182 patients with

recurrent GBM. The patients who received combined therapy had an equivalent duration of 10.1 months, while those who received bevacizumab alone had a duration of 9.7 months. observed median survival duration; yet, a superior 6-month progression-free survival was linked to combination treatment [3]. Since 2009, BEV has been the accepted salvage therapy for individuals with recurrent GBM [14]. Because of its generally low toxicity profile and strong blood-brain barrier penetration, temozolomide is widely utilized as rescue therapy. PFS for recurrent GBM is approximately 15.5 months on average [18]. The PFS of patients receiving first-line TMZ in our trial was found to be 6 months, which was less than expected. It's possible that because this regimen is recommended for patients with grade 3 and lower grades, the PFS of patients undergoing TMZ rechallenge is longer than that of patients receiving BEV + IRI.

The most important limitations of our study were the small number of patients receiving systemic treatment after relapse and the limited number of patients receiving targeted treatment.

Limitation

The low number of recurrent patients is a limitation of our study because the nature of the disease results in short survival.

Conclusion

As a result, systemic treatment effectiveness is poor for these patients. Curative outcomes are rare with treatment. The impact of the proposed treatment on performance status and quality of life ought to be taken into account, regardless of the severity of the disease. Evaluation of progression-free survival durations revealed no statistically significant difference between therapies; hence, individuals with gliomas that do not exhibit targetable pathological changes may benefit from active surveillance or a less hazardous regimen. Individualized treatments need to be created. Large-phase studies investigating genetic mutations are needed to develop targeted therapies.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and Human Rights Statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or compareable ethical standards.

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Conflict of Interest

The authors declare that there is no conflict of interest.

References

1. Kosianova A, Pak O, Bryukhovetskiy I. Regulation of cancer stem cells and immunotherapy of glioblastoma (Review). Biomed Rep. 2023;19;20(2):24.

2. Yu MW, Quail DF. Immunotherapy for Glioblastoma: Current Progress and Challenges. Front Immunol. 2021;13;12:676301.

3. McBain C, Lawrie TA, Rogozińska E, Kernohan A, Robinson T, Jefferies S. Treatment options for progression or recurrence of glioblastoma: a network meta-analysis. Cochrane Database Syst Rev. 2021;5(1):CD013579.

4. Horbinski C, Nabors LB, Portnow J, et al. NCCN Guidelines® Insights: Central Nervous System Cancers, Version 2.2022. J Natl Compr Canc Netw. 2023;21(1):12-20.

5. Angom RS, Nakka NMR, Bhattacharya S. Advances in glioblastoma therapy: An update on current approaches. Brain Sci. 2023;31;13(11):1536.

6. Hundsberger T, Reardon DA, Wen PY. Angiogenesis inhibitors in tackling recurrent glioblastoma. Expert Rev Anticancer Ther. 2017;17(6):507-515.

7. Lombardi G, De Salvo GL, Brandes AA, et al. Regorafenib compared with lomustine in patients with relapsed glioblastoma (REGOMA): A multicentre, open-label, randomised, controlled, phase 2 trial. Lancet Oncol. 2019;20(1):110-119.

8. Doebele RC, Drilon A, Paz-Ares L, et al. Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: Integrated analysis of three phase 1-2 trials. Lancet Oncol. 2020;21(2):271-282.

9. Bourque MS, Salek M, Sabin ND, Canale M, Upadhyaya SA. Comment on: Response to the BRAF/MEK inhibitors dabrafenib/trametinib in an adolescent with a BRAF V600E mutated anaplastic ganglioglioma intolerant to vemurafenib. Pediatr Blood Cancer. 2021; 68(4):e28814.

10. Kaley T, Touat M, Subbiah V, et al. BRAF ınhibition in BRAFV600-mutant gliomas: Results from the VE-BASKET study. J Clin Oncol. 2018; 10;36(35): 3477-3484.

11. Oppenlander ME, Wolf AB, Snyder LA, et al. An extent of resection threshold for recurrent glioblastoma and its risk for neurological morbidity. J Neurosurg. 2014; 120(4):846-53.

12. Hong B, Wiese B, Bremer M, et al. Multiple microsurgical resections for repeated recurrence of glioblastoma multiforme. Am J Clin Oncol. 2013; 36(3):261-8.

13. Minniti G, Niyazi M, Alongi F, Navarria P, Belka C. Current status and recent advances in reirradiation of glioblastoma. Radiat Oncol. 2021;18;16(1):36.

14. Friedman HS, Prados MD, Wen PY, et al. bevacizumab alone and in combination with ırinotecan in recurrent glioblastoma. J Clin Oncol. 2023; 10;41(32):4945-4952.

15. Navarria P, Minniti G, Clerici E, et al. Re-irradiation for recurrent glioma: outcome evaluation, toxicity and prognostic factors assessment. A multicenter study of the Radiation Oncology Italian Association (AIRO). J Neurooncol. 2019; 142(1):59-67.

16. Ali AS, Chen VE, Zurlo C, Taylor JM, Fernandez C, Shi W. Target treatment with stereotactic radiation for recurrent gliomas. Chin Clin Oncol. 2020; 9(6):74.

17. Chapman CH, Hara JH, Molinaro AM, et al. Reirradiation of recurrent high-grade glioma and development of prognostic scores for progression and survival. Neurooncol Pract. 2019; 6(5):364-374.

18. Schaff LR, Mellinghoff IK. Glioblastoma and other primary brain malignancies in adults: A review. JAMA. 2023; 21; 329(7):574-587.

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